



Original Research

Intraperitoneal bevacizumab for control of malignant ascites due to advanced-stage gastrointestinal cancers: A multicentre double-blind, placebo-controlled phase II study – AIO SUP-0108



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Abstract Purpose: Malignant ascites is debilitating for patients with advanced cancer. As shown previously, tumour cell production of vascular endothelial growth factor might be a major cause of the formation of malignant ascites. Intraperitoneal bevacizumab could therefore be an option for symptom control in refractory ascites.

Patients and methods: Patients with advanced gastrointestinal cancer and malignant ascites who had undergone paracentesis at least twice within the past 4 weeks were randomly assigned in a 2:1 ratio to intraperitoneal bevacizumab (400 mg absolute) or placebo after paracentesis. During the 8-week treatment period, a minimum interval of 14 d was kept between the applications of the study drug. Primary end-point was paracentesis-free survival (ParFS).

Results: Fifty-three patients (median age 63 years) were randomised. Forty-nine patients received at least one study drug application and qualified for the main analysis. The

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proportion of patients with at least one common toxicity criteria grade III–V event was similar with 20/33 (61%) on bevacizumab and 11/16 (69%) on placebo. Median ParFS was 14 d (95% confidence interval [CI]: 11–17) in the bevacizumab arm and 10.5 d (95% CI: 7–21) on placebo (hazard ratio 0.74, 95% CI: 0.40–1.37; $P = 0.16$). The longest paracentesis-free period was 19 d on bevacizumab (range 6–66 d) and 17.5 d in the placebo arm (range 4–42) ($P = 0.85$). Median overall survival was 64 d (95% CI: 45–103) on bevacizumab compared to 31.5 d (95% CI: 20–117) on placebo ($P = 0.31$).

Conclusion: Intraperitoneal bevacizumab was well tolerated. Overall, treatment did not result in a significantly better symptom control of malignant ascites. However, patients defined by specific immune characteristics may benefit.

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1. Introduction

Despite major prognostic improvements in the palliative treatment of patients with gastrointestinal cancer, symptomatic malignant ascites, which occurs in up to 15% of these patients, remains a challenge in optimal symptom management [1]. Fluid accumulation causes severe impairing symptoms [2]. Its elimination is a foremost goal and generally improves the patient's quality of life, or even may prolong survival [3]. Diuretic therapy is effective in the beginning. Alternative options such as intraperitoneal chemotherapy or targeted therapies need further investigation.

With progressive disease, the fluid recurrence usually accelerates, requiring more frequent paracenteses. Stringently designed, randomised trials in this area are rare. Except for catumaxomab, a trispecific monoclonal antibody prolonging puncture-free periods [4], there is a general lack of evidence on efficacy [2,5,6]. However, catumaxomab is at present not generally available anymore.

Besides mechanical obstruction and hormonal effects, cytokine release seems to play a major role in the pathophysiology of malignant ascites [1,6]. Recently translational research as well as clinical results from small case series have suggested a potential role of the vascular endothelial growth factor (VEGF) in the development process of malignant ascites [1,7].

The rationale of this placebo-controlled randomised phase II study was to assess, whether the intraperitoneal administration of the monoclonal anti-VEGF antibody bevacizumab is able to impact on development of malignant ascites in order to improve symptom control in patients with advanced gastrointestinal cancer.

2. Patients and methods

2.1. Study design

This multicentre, placebo-controlled, double-blind randomised phase II study was carried out according to the

Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the appointed Ethical Committee of each participating site. Written informed consent was obtained from all patients before study participation. Registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01200121) NCT01200121.

2.2. Patient population

Patients aged ≥ 18 years with histologically confirmed gastrointestinal cancer, with ascites were eligible. Malignant ascites had to be diagnosed either cytologically, or as an exudate with total protein >30 g/L clinically suggestive for malignant origin, or morphologically as peritoneal carcinosis by imaging. Ascites had to be clinically assessed to be non-responsive to both conventional systemic treatment of the underlying disease, and to diuretics, demanding at least two previous paracenteses within 4 weeks prior to enrolment were required. Further inclusion criteria were Eastern Cooperative Oncology Group performance score ≤ 3 , a life expectancy of at least 12 weeks, and no severe abnormalities with respect to haematology, clinical chemistry and urinalysis parameters. Major exclusion criteria were bacterial peritonitis, haemorrhagic ascites, initiation of new treatment with other antineoplastic agents as already applied before inclusion (continuation of ongoing treatment which did not result in sufficient ascites control was permitted), parallel treatment with bevacizumab intravenous (i.v.), and standard contraindications preventing bevacizumab treatment.

2.3. Treatment plan and assessments

Bevacizumab and placebo medication were manufactured centrally, securing blind allocation to the study patients following a concealed, computer-generated randomisation list, in a 2:1 ratio.

Before inclusion of a patient into the study, a 4-week screening period allowed for a stringent evaluation of the patient regarding fulfilment of inclusion and exclusion criteria (Fig. 1). In eligible patients the treatment

period started with the application of the first paracentesis with study medication. The indication for the following paracenteses was assessed by the treating physician as needed for symptom control. With those, up to four intraperitoneal administrations of bevacizumab (400 mg absolute dose in 100 ml NaCl 0.9%) or placebo with a minimum interval of 14 d following subsequent paracenteses, during a maximum period of 8 weeks were administered, after placement of an intraperitoneal catheter and removal of the maximum volume of ascites for symptom relief. In case of unacceptable toxicity, treatment was prematurely discontinued. The following assessments were performed before or after each study paracentesis and 4 weeks thereafter: volume of ascites drained, performance status, physical examination, body weight, quality of life using the Functional Assessment of Chronic Illness Therapy-Ascites Index (FACIT-AI) questionnaire [8], supportive procedures, urinalysis, haematology, clinical chemistry, activated partial thromboplastin time (aPTT), international normalized ratio (INR), and adverse events. Further puncture-free and overall survival (OS) follow-up took place every 2 months for 1 year.

2.4. End-points and statistical aspects

The first primary end-point was paracentesis-free survival (ParFS), i.e. the time from randomisation to either the second on-study paracentesis or to death, whichever occurred first. Based on results by Heiss *et al.* [4] the median ParFS in the untreated control group was expected to be approximately 14 d. In order to detect a doubling of this interval to a median of 28 d by bevacizumab (hazard ratio [HR]: 0.5), a total number of 60 evaluable patients (40 in the experimental group, 20 in the control group, according to the 2:1 randomisation) with their event observed was required with a one-sided type I error of 5% and a power of 80%. In order to allow

for non-evaluable cases or drop-outs, a total of 72 patients were planned to be randomised. A second primary end-point ('best response') was defined as the longest paracentesis-free period within the 12-week main observation period.

Secondary study end-points included: number of paracenteses during the 12-week observation period; quality of life; changes in performance status; OS, defined as the time from randomisation until death; rates of adverse events graded according to NCI common toxicity criteria (CTC) V. 3.0. Time-to-event data were analysed by the Kaplan–Meier method and compared using the log-rank test [9]. Other continuous data were compared using the Wilcoxon–Mann–Whitney test. Within-group comparisons between different time points or periods, were performed with the Wilcoxon signed rank test. All tests except for the primary end-points were considered explorative and are two-sided.

2.5. Luminex analysis

Ascites samples were collected from patients at the time of baseline paracentesis and after a median of 2 weeks (range 1–3 weeks) after administration of the first dose of the study drug with the second routine paracentesis. Samples were centrifuged at 1000 g for 10 min and frozen at a minimum of -20°C until further use. Luminex analyses were performed according to the manufacturer's instructions by EMD Millipore.

3. Results

3.1. Patient population and screening paracenteses

Between June 2010 and July 2013, a total of 157 patients had been screened and 53 patients from 14 institutions in Germany were randomised (Fig. 2). Due to the unexpectedly low rate of patients eventually fulfilling the

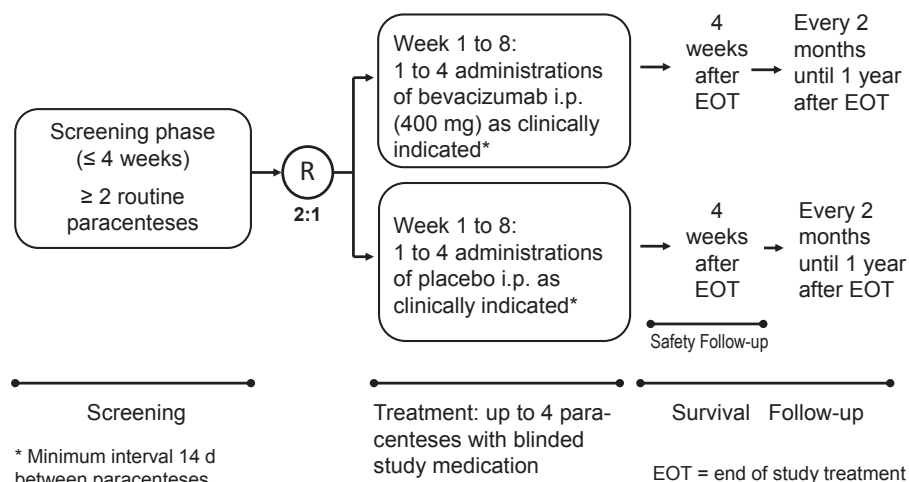


Fig. 1. Study flowchart. *Minimum interval of 14 d between paracenteses with study drug administration. EOT = end of study treatment.

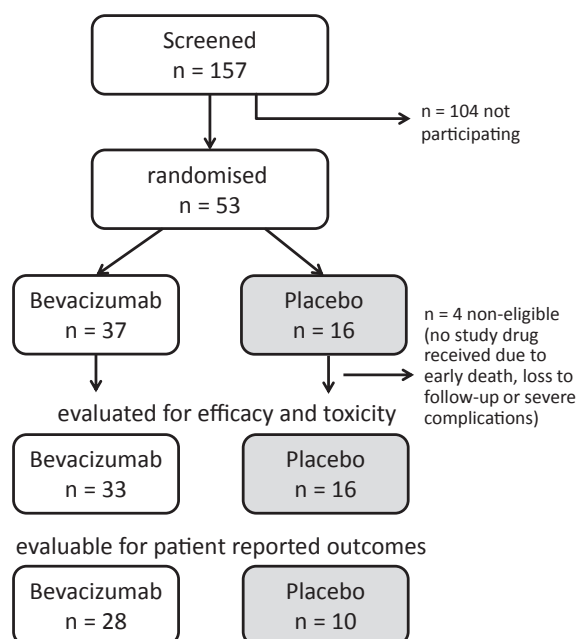


Fig. 2. Overview of patient disposition.

eligibility criteria for randomisation, the study had to be closed for recruitment prematurely. The most frequent reason for non-inclusion was a deterioration of the general condition during screening, followed by failure to gain informed consent, and a too low frequency of paracentesis. Baseline demographic and clinical characteristics are described in Table 1. The majority of the

patients had pancreatic cancer. Inevitably, due to the small patient numbers, some imbalances are present between the groups, but paracentesis history parameters were rather equally distributed.

3.2. Treatment exposure

Of the 208 recorded paracenteses during the observation period 55% were followed by the administration of study medication. Twenty percent of the patients received the maximum number of four applications, with rather equal increments of the study population receiving one (bevacizumab/placebo: 30/38%, respectively), two (21/25%), three (30/12%) or four applications (18/25%). Premature termination was mainly caused by death (overall: 43%; bevacizumab: 39%, placebo: 50%). Other reasons included withdrawal of consent ($n = 1$), patient's request ($n = 2$), investigator's decision ($n = 3$), or switching to a non-protocol ascites treatment ($n = 1$).

3.3. Efficacy

The median numbers of interventional paracenteses during the study period were 4 (range: 1–17) and 3 (range: 1–8) for bevacizumab or placebo, respectively. ParFS curves as the primary efficacy criterion are shown in Fig. 3A, based on observed events in all of the 49 evaluable patients. There was no major difference between the bevacizumab and the control group with

Table 1
Baseline characteristics and screening paracenteses.

Category	Study arm	
	Bevacizumab ($n = 33$)	Placebo ($n = 16$)
Age, median (range) [years]	62 (35–81)	65.5 (46–75)
Gender, female [n (%)]	15 (45)	4 (25)
Cancer type [n (%)]		
– Cholangiocellular	1 (3)	3 (19)
– Colorectal	5 (15)	1 (6)
– Gastric	9 (27)	1 (6)
– Hepatocellular	1 (3)	–
– Pancreatic	17 (52)	10 (62)
– Unknown primary (Adeno-Ca)	–	1 (6)
Time since initial diagnosis of cancer, median [months]	9.9	12.1
Time since initial diagnosis of disseminated disease, median [months]	9.1	11.9
Number of previous antineoplastic regimens, median	2	2
Performance status [n (%)] (missing in three patients)		
ECOG 0–1	15 (45)	4 (25)
ECOG 2	12 (36)	9 (56)
ECOG 3	5 (15)	1 (6)
Paracenteses during screening period (4 weeks):		
Number, median (range)	2 (1 ^a –10)	2 (1 ^a –4)
Average interval between paracenteses, median (range) [d]	8 (1.1–17)	8 (3.5–16.3)
Maximum interval between paracenteses, median (range) [d]	10 (2–27)	11.5 (6–27)
Average ascites volume of last two paracenteses, median	3550	3250

ECOG, Eastern Cooperative Oncology Group.

^a Following a late protocol amendment, patients were allowed to be randomised in case of only one instead of two paracenteses during screening. However, in the end only two patients had been randomised with merely one screening paracentesis.

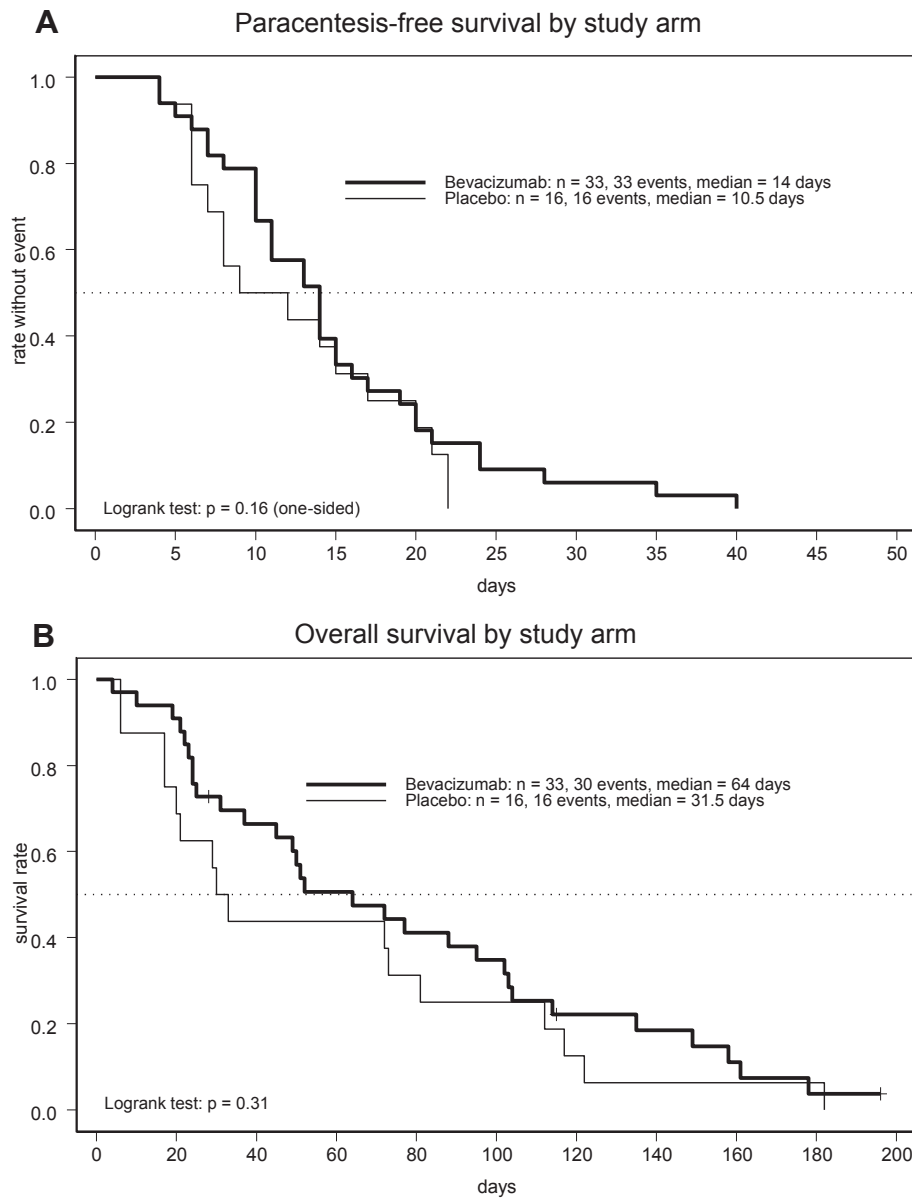


Fig. 3. Paracenteses-free (A) and overall survival (B).

ParFS medians of 14.0 d (95% confidence interval [CI]: 11–17 d) and 10.5 d (7–21 d). The HR amounts to 0.74 (95% CI: 0.40–1.37, $P = 0.16$). Thus, the CI does not exclude the prospectively anticipated target effect size of HR = 0.5. The ParFS result was clearly dominated by paracentesis events, as in only eight patients (16%) death occurred first before a second on-study paracentesis. Likewise, the second primary efficacy end-point, ‘best response’, did not show any major benefit in the bevacizumab group, with a mean maximum period without paracentesis of 22.9 d in the bevacizumab arm (median: 19, range: 6–66 d) versus 18.7 d in the placebo arm (median: 17.5, range 4–42 d; $P = 0.85$).

In respect to OS the Kaplan–Meier estimates suggest a moderate trend in favour of bevacizumab (HR: 0.73,

95% CI: 0.40–1.37), without reaching statistical significance ($P = 0.31$, Fig. 3B).

3.4. Effect of intraperitoneal bevacizumab treatment on ascites cytokine/chemokine levels

Using Luminex technology, 13 soluble factors were analysed in ascites samples from 22 patients of whom pre- and post-treatment samples were available (Fig. 4A). Overall, no significant changes in cytokine/chemokine levels were detected. However, in the group treated with bevacizumab we observed 8/16 patients with at least 75% reduced ascites VEGF levels compared to 0/6 patients in the placebo group. Within the patient group treated with bevacizumab we further observed a

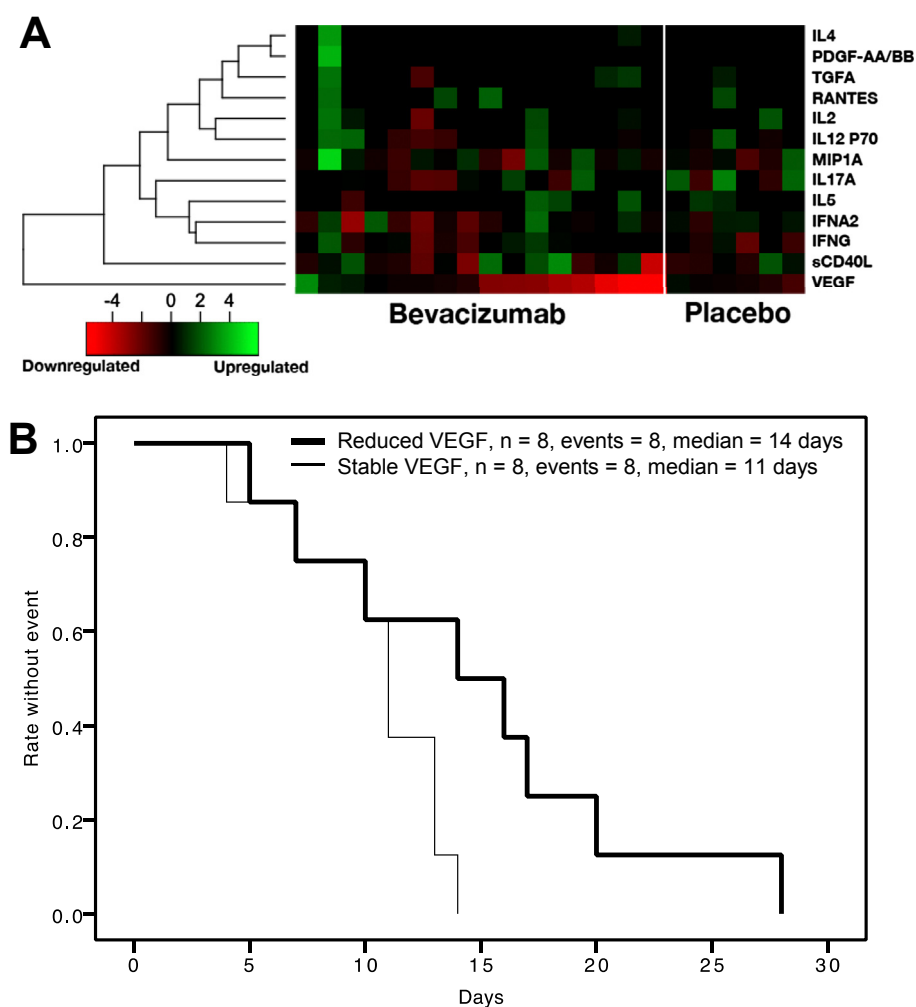


Fig. 4. Cytokine levels in patients treated with bevacizumab or placebo. (A) Logarithmic fold changes of cytokines in ascites samples 2 weeks after initial paracentesis compared to the patients' respective samples before treatment. (B) Paracentesis-free survival of patients with ascites VEGF levels reduced by more than 75% compared to patients with ascites VEGF levels reduced by less than 75%. VEGF, vascular endothelial growth factor; IL, interleukin; PDGF, platelet derived growth factor; TGF, transforming growth factor; RANTES, regulated on activation, normal T-expressed, and presumably secreted; MIP, Macrophage Inflammatory Protein 1 alpha; IFNA, Interferon alpha; IFNG, Interferon gamma.

slightly prolonged median ParFS (Fig. 4B) in those patients experiencing at least a 75% reduction in ascites VEGF levels after treatment, compared to patients with more stable VEGF levels.

3.5. Safety

Due to the end-stage cancer status of all patients, a plethora of adverse events were recorded with questionable relation to the study medication. The overall frequency of events of CTC severity grades III–V was not higher under bevacizumab (61%) than in the placebo arm (69%). No case of hypertension was reported in either treatment arm. One serious thromboembolic event was reported in both arms (bevacizumab: 3%; placebo: 6%). Gastrointestinal symptoms occurred more

often in the bevacizumab group, with nausea reported in 45% versus 31%, and vomiting in 36% versus 0%. Almost all of the recorded deaths were caused by progressive tumour disease (96%).

3.6. Patient reported outcomes and supportive procedures

According to the specifications of the FACIT-AI, a summary score was calculated from the 13 items, ranging from 0 (worst) to 52 (best). Assessment of quality of life was inevitably compromised by the major loss process in this highly palliative situation. While 78% of the forms were available at randomisation, the questionnaires for week 8 were available in only 24% of the patients. At baseline, i.e. before the first on-study paracentesis, the total population showed a relevant

deterioration of health status due to ascites, with a median score of 31 with a rather low variability (inter-quartile range: 27–36). All pairwise comparisons of the FACIT-AI between study weeks 0, 2 and 4 did not indicate any significant difference (all P values >0.3), in both arms as well as in the total population.

4. Discussion

This study is the first to test, in a randomised blinded design, the potential benefit of intraperitoneal administration of bevacizumab, in order to evaluate this approach as a treatment option for symptom control in the difficult treatment situation of advanced recurrent ascites.

Bevacizumab was chosen as it is known that VEGF plays a decisive role – not only in angiogenesis but also in the pathophysiology of malignant ascites, by augmenting the permeability of microvasculature and of the peritoneal membrane [7,10,11]. In animal models, the expression level in cancer cells was markedly associated with the production of ascites, while VEGF injections increased the permeability of pre-existing small vessels lining the peritoneum. Following promising data on peritoneal influx blocking and impressive ascites remissions in *in vivo* models [7], a number of clinical case series provided beneficial results for bevacizumab, especially when given intraperitoneal (i.p.), in patients with ascites secondary to a variety of solid tumours, predominantly ovarian cancer. However, the sample sizes were rather small, ranging from 1–9 patients [7,12]. For the largest series, published in abstract form, El-Shami *et al.* reported resolution or at least distinctly delayed reaccumulation of ascites in all of the nine patients enrolled, after only one i.p. application of 5 mg/kg bevacizumab [13].

Those results stimulated the prospective and controlled evaluation of i.p. administration in our trial. One hypothesis was that i.p. application should build up the highest concentration of the study drug within the body compartment where malignant ascites is promoted by VEGF secretion. Secondly, it is assumed that i.p. agents are readily absorbed by the peritoneal tumour tissue. Thirdly, this route was likewise successfully used in most pre-clinical animal models [7,14].

The overall median ParFS, based on observed events in all patients, was 13 d for the whole study population (95% CI: 10–15 d). This is in accordance with the assumed median of 14 d, which formed the basis for the statistical design calculation of the trial. Nevertheless, our observations could not confirm the benefits suggested by the pilot studies, both with respect to the time to the next recurrence event nor to the duration of the subsequent paracentesis. Likewise, no major differences between bevacizumab and placebo could be detected in the secondary clinical or patient-reported outcomes. However, it might be of

interest that we did observe a trend towards an improved event-free survival in those patients evidencing a substantial decrease in VEGF levels in their malignant ascites following bevacizumab treatment. A recently published abstract on a retrospective series of 34 patients, without control group, with ascites secondary to gynaecological or gastrointestinal cancers, suggested some prolongation of ParFS in exudative but not transudative types of ascites [15].

The poor median survival of about 1–2 months in our overall population is quite in agreement with the results from other similar patient series, i.e. with the gastric cancer control group, experiencing recurrent punctures, in the randomised catumaxomab trial [4], and with the 3 months counted from first detection of ascites in gastrointestinal cancer patients by Ayantunde *et al.* [5].

In our study, the far advanced stage of ascites, in combination with the short remaining lifetime, possibly associated to the predominance of pancreatic cancer in our cohort (55%, compared to only 7% in the catumaxomab study), may have prevented the detection of a meaningful efficacy of the tested agent. Alternatively, the chosen i.p. treatment could be suboptimal in this setting [16]. Meanwhile, more promising results became available from controlled studies on the effect of VEGF-targeting therapies in ovarian cancer. In a randomised study with 55 patients with ascites, i.v. aflibercept, an inhibitor of both VEGF and placental growth factor proved to be superior compared to placebo for the time to repeat paracentesis but with an increased risk of intestinal perforations [17]. The large randomised AURELIA and GOG 0218 studies on i.v. bevacizumab (which enrolled also patients without ascites) show beneficial progression-free and OS effects in the subgroups with ascites [18,19]. However, in ovarian cancer, the amount of ascites is comparatively small, especially in the first-line setting, in which the ascites is often detected (and removed) during surgery. In addition, bevacizumab was given in combination with newly-introduced chemotherapy.

A general drawback is the lack of standard definitions of end-points in this disease setting, and their subjectivity and variability between investigators. Unfortunately, the number of samples available for extended translational analysis was limited. Nevertheless, there is some hint of a correlation of reduced ascites VEGF level development in the bevacizumab group, and slightly prolonged ParFS.

In conclusion, in this unfavourable group of patients with far advanced disease and refractory ascites, i.p. bevacizumab was well tolerated. However, the i.p. administration in addition to paracentesis did neither result in a better symptom control of malignant ascites nor in a significant prognostic improvement in patients with advanced gastrointestinal cancer.

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Conflict of interest statement

The authors have following conflict of interests to disclose:

KJ: Consulting or advisory role (Merck, MSD and Helsinn, Tesaro).

T.K.: Nothing to disclose.

CG: Nothing to disclose.

BK: Research funding (Roche, Novartis), travel cost reimbursement (Teva, Lilly, Roche, Boehringer Ingelheim).

DArnold: Consulting or advisory role (Roche, Fresenius Biotech, Merck Serono, Bayer Healthcare, Amgen).

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WF: Nothing to disclose.

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SHB: Consulting or advisory role (Roche).

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References

- [1] Smith EM, Jayson GC. The current and future management of malignant ascites. *Clin Oncol* 2003;15:59–72.
- [2] Walton L, Nottingham JM. Palliation of malignant ascites. *J Surg Educ* 2007;64:4–9.
- [3] Rosenberg SM. Palliation of malignant ascites. *Gastroenterol Clin North Am* 2006;35:189–99.
- [4] Heiss MM, Murawa P, Koralewski P, Kutarska E, Kolesnik OO, Ivanchenko VV, et al. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: results of a prospective randomized phase II/III trial. *Int J Cancer* 2010;127:2209–21.
- [5] Ayantunde AA, Parsons SL. Pattern and prognostic factors in patients with malignant ascites: a retrospective study. *Ann Oncol* 2007;18:945–9.
- [6] Becker G, Galandi D, Blum HE. Malignant ascites: systematic review and guideline for treatment. *Eur J Cancer* 2006;42:589–97.
- [7] Kobold S, Hegewisch-Becker S, Oechsle K, Jordan K, Bokemeyer C, Atanackovic D. Intraperitoneal VEGF inhibition using bevacizumab: a potential approach for the symptomatic treatment of malignant ascites? *Oncologist* 2009;14:1242–51.
- [8] Cella D, Neubauer N, Thomas J, Kutner J, Seiden MV. The FACIT-AI, a new tool for assessing symptoms associated with malignant ascites. *Gynecol Oncol* 2013;128:187–90.
- [9] Peto R, Peto J. Asymptotically efficient rank invariance test procedures (with discussion). *J R Stat Soc A* 1972;135:185–206.
- [10] Nagy JA, Herzberg KT, Dvorak JM, Dvorak HF. Pathogenesis of malignant ascites formation: initiating events that lead to fluid accumulation. *Cancer Res* 1993;53:2631–43.
- [11] Kipps E, Tan DSP, Kaye SB. Meeting the challenge of ascites in ovarian cancer: new avenues for therapy and research. *Nat Rev Cancer* 2013;13:273–82.
- [12] Fushida S, Oyama K, Kinoshita J, Yagi Y, Okamoto K, Tajima H, et al. VEGF is a target molecule for peritoneal metastasis and malignant ascites in gastric cancer: prognostic significance of VEGF in ascites and efficacy of anti-VEGF monoclonal antibody. *Onco Targets Ther* 2013;6:1445–51.
- [13] El-Shami K, Elsaid A, El-Kerm Y. Open-label safety and efficacy pilot trial of intraperitoneal bevacizumab as palliative treatment in refractory malignant ascites. *J Clin Oncol* 2007;25(Suppl.):9043.
- [14] Imaizumi T, Aoyagi K, Miyagi M, Shirouzu K, Dreyer C, Faivre SJ, Raymond E. Suppressive effect of bevacizumab on peritoneal dissemination from gastric cancer in a peritoneal metastasis model. *Surg Today* 2010;40:851–7.
- [15] Mateescu C, Becq A, Bouattour M, Dreyer C, Faivre SJ, Raymond E, et al. Bevacizumab administered intraperitoneally as palliative treatment of malignant refractory ascites. *J Clin Oncol* 2014;32(Suppl.):e20617.
- [16] Woopen H, Schouli J. Current and future options in the treatment of malignant ascites in ovarian cancer. *Anticancer Res* 2009;29:3353–60.
- [17] Gottlieb WH, Amant F, Advani S, Goswami C, Hirte H, Provencher D, et al. Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. *Lancet Oncol* 2012;13:154–62.
- [18] Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol* 2014;32:1302–8.
- [19] Ferriss JS, Java JJ, Bookman MA, Fleming GF, Monk BJ, Walker JL, et al. Ascites predicts treatment benefit of bevacizumab in front-line therapy of epithelial ovarian, fallopian tube and peritoneal cancers: an NRG Oncology/GOG study. *Gynecol Oncol* 2015. <http://dx.doi.org/10.1016/j.ygyno.2015.07.103> [Epub ahead of print].